that the statement of the substance of the interview filed in the October 27 Amendment complies with Applicants' requirement to record the substance of the interview.

Claim Rejection- 35 U.S.C. 103

Claims 15, 16, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hidaka et al., (US 5,972,976) in view of Goodman and Gilman (1996). Applicants respectfully request reconsideration of the rejection.

Claim 27 is directed to a method for treating a patient suffering from at least one malignant tumor selected from the group consisting of blood cancer, leukemia, human colon adenocarcinoma, gastrointestinal cancer, lung caner, breast cancer, and prostate cancer. The method comprises administering a therapeutically effective amount of (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]ethenyl]pyridine1-oxide (referred to as HMN-214 hereinafter) or a pharmaceutically acceptable salt thereof in combination with cisplatin. Claim 27 also recites that the therapeutically effective amount of (E)-4-[2-[2-[N-acetyl-N-[(p-methoxyphenyl)sulfonyl]amino]phenyl]pyridine 1-oxide with cisplatin gives a synergistic inhibitory effect.

Regarding the evidence of record on synergism, Applicants respectfully disagree with the conclusions stated in the Office Action and provide the following additional clarifications. The T/C (%) values represent survival rate, and the values reported by Applicants do reflect of synergism. For clarification, the T/C (%) values are calculated from ([the median survival time (MST) of a treated group (T)] ÷ [MST of a control group (C)]) x 100, e.g. as explained at page 22, lines 22-27 and shown in Table 1 of the specification as filed.

With further reference to Table 1, mice of a control group can survive for 10 days without any antitumor drugs, which provides the reference T/C (%) value of 100%, by which the other tests are compared. When 50 mg of Compound 2 (i.e., HMN-214) was administered alone to mice, who have a survival time of 10 days, MST of mice was 13 days in Table 1, which shows that Compound 2 alone can extend the survival of mice by 13 – 10 = 3 days. Therefore, with respect to the survival rate T/C(%) when Compound 2 was administered alone, the following calculation T(13)/C(10) x 100 = 130%, which is 30% higher than the control group.

Similarly, when 5 mg of CDDP (i.e., cisplatin) was administered alone to mice who have survival time of 10 days, MST of mice was 17 days in Table 1, which shows that CDDP alone can extend the survival of mice by 17 -10 = 7 days. Therefore, with respect to survival rate T/C(%) when CDDP was administered alone, the following calculation T(17)/C(10) x 100 = 170%, which is 70% higher than the control group.

The additive effect of these two results provides a 100% higher survival rate than the control group, i.e. 30% (for HMN-214) + 70% (for cisplatin). That is, the effect of the combined administration based on the above, would be expected to provide at most a survival rate extended by 3 + 7 = 10 days compared to a control group. When stated in terms of the calculation for T/C(%), T(10 + 10)/C(10) x 100 = 200%, or 100% above the control.

However, Applicants have shown that synergistic effects, not mere additive effects, are observed. For example, when a combination of 50 mg of Compound 2 (i.e., HMN-214) and 5 mg of CDDP (i.e., cisplatin) is administered, the survival rate is significantly higher than what is expected by the additive effect. As reported by Applicants in Table 1, T/C(%) of Compound 2 (50 mg) + CDDP (5 mg) exhibited a survival rate of 240%, which is significantly higher than the expected 200%. In other words, the extended survival of mice would be 14 days, not the additive 10 days. Such extended survival effects of the claimed combination administration represent a synergistic effect, not a mere additive effect.

With further reference to Table 1, a combined administration of 10 mg of CDDP of day 1 and 100 mg of Compound 2 of day 2 extended survival of mice by >50 as shown in Table 1, or >40 days when compared to a control group. See MST value in Table 1. By way of comparison, if the combined administration were to provide an additive effect for the same dosages, then the extended survival of mice (see MST values for corresponding dosages and relative to the control) would be (17– 10) + (15 – 10) = 12 days. However, this is not the case as shown by the effects of the combined administration when compared to the sum of the single administrations. Thus, the results further support the synergism found in the invention of claim 27.

For at least these reasons, the method of claim 27 provides unexpected results that could not have been expected based on any combination of Hidaka et al., Goodman and Gilman.

Moreover, there is no suggestion that one of skill in the art would have any reasonable expectation of success administering the compounds as in claim 27. The Office Action alleges that Goodman and Gilman disclose that cisplatin may be combined with other anticancer drugs for the treatment of cancers, and drugs are generally more effective in combination and may be synergistic through biochemical interactions (see pages 1229-1230). However, Goodman and Gilman disclose or suggest a very limited number of anticancer drugs only which may be combined with cisplatin. Specifically, Goodman and Gilman disclose that combination chemotherapy with cisplatin, bleomycin, etoposide, and vinblastine is curative for...advanced testicular cancer, and the drug is also beneficial in carcinoma...when used with paclitaxel, cyclophosphamide, or doxorubicin (see page 1270). Among the "other anticancer drugs", bleomycin, etoposide, cyclophosphamide and doxorubicin act as a DNA synthesis inhibitor, and vinblastine and paclitaxel act as a microtubule polymerization inhibitor.

The claimed HMN-214, however, has a different mechanism of action than the compounds disclosed by Goodman and Gilman. For example, HMN-214 can act on sites other than microtubule, and thereby induces apoptosis specifically during M phase (see page 10, lines 11-13 of the Applicants' specification).

Furthermore, HMN-214 is the prodrug form of HMN-176, ((E)-4-{[2-N-[4-methoxybenzenesulfonyl]amino]stilbazole}1-oxide), which is an active metabolite of HMN-214, also shows a different mechanism as an anticancer drug (see Michael A. DiMaio, et al. Mol Cancer Ther 2009;8(3) which is submitted herewith). DiMaio et al. reported that HMN-176 can inhibit centrosome-dependent MT (microtubule) assembly, thereby inhibiting normal progression through the mitotic phase of the cell cycle and ultimately leading to cell death (see page 600, left column, lines 29-32 of DiMaio et al.). Such centrosome-dependent mechanism is also quite different from mechanisms of the other anticancer drugs disclosed in Goodman and Gilman, and a centrosome-dependent mechanism is not disclosed or suggested in Goodman and Gilman. Given the differences in the mechanisms of the compounds, there is nothing in the references to establish any

reasonable expectation of success upon administering the compounds as claimed in claim 27.

Consequently, claim 27 and its dependents do not follow from the references cited and are patentable for at least the foregoing reasons. Favorable reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above remarks, Applicants respectfully request favorable reconsideration of this application in the form of a Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative listed below.

Respectfully submitted,

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